

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/GB2004/002827

International filing date (day/month/year)
28.06.2004

Priority date (day/month/year)
28.06.2003

International Patent Classification (IPC) or both national classification and IPC
C07K14/52, C07K14/61, C12N15/10, C12N15/86, C12N5/10, A01K67/027, A61K38/27, A61K38/19, A61K48/00

Applicant
ASTERION LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/002827

IAP20 RECEIVED PTO 21 DEC 2005

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☒ furnished subsequently to this Authority for the purposes of search.
3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/002827

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 51 and 53 partially

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 51 and 53 partially

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/002827

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	3, 14-23, 28-40, 50, 52
	No: Claims	1, 2, 4-13, 24-27, 41-49, 53
Inventive step (IS)	Yes: Claims	3, 14-23, 28-40, 50, 52
	No: Claims	
Industrial applicability (IA)	Yes: Claims	3, 14-23, 28-40, 50, 52
	No: Claims	

2. Citations and explanations

see separate sheet

IAP20 Rec'd PCT/GB 21 DEC 2005

Re Item V**Reasoned statement with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

Reference is made to the following documents:

- D1: DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1995, KREITMAN ROBERT J ET AL: "Circularly permuted interleukin 4 retains proliferative and binding activity" XP002325867 Database accession no. PREV199598326840
- D2: HORLICK R A ET AL: "PERMUTEINS OF INTERLEUKIN 1 BETA-A SIMPLIFIED APPROACH FOR THE CONSTRUCTION OF PERMUTATED PROTEINS HAVING NEW TERMINI" PROTEIN ENGINEERING, OXFORD UNIVERSITY PRESS, SURREY, GB, vol. 5, no. 5, 1992, pages 427-431, XP002022097 ISSN: 0269-2139
- D3: US-A-5 635 599 (PASTAN ET AL) 3 June 1997 (1997-06-03)
- D4: MCWHERTER C A ET AL: "Circular permutation of the granulocyte colony-stimulating factor receptor agonist domain of myelopoietin" BIOCHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, PA, US, vol. 38, no. 14, 6 April 1999 (1999-04-06), pages 4564-4571, XP002131431 ISSN: 0006-2960
- D5: WO 00/18905 A (G.D. SEARLE & CO; LEE, STEPHEN, C) 6 April 2000 (2000-04-06)
- D6: US-A-6 136 563 (CUNNINGHAM ET AL) 24 October 2000 (2000-10-24)

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1, 2, 4-13, 24-27, 41-49, 53 is not new in the sense of Article 33(2) PCT.

The document D1 discloses circularly permuted IL-4 mutants comprising a linker (GGNGG) joining the carboxyl to the amino terminus and new carboxyl and amino termini in a new position on the protein (see abstract). The IL-4 mutants retained 50-100% of the binding and proliferative activity of IL-4 (see abstract).

D2 discloses methods for the construction of permuted proteins, in particular, IL-1 β . The mutant IL-1 β proteins have the N and C-termini ligated together using an amino acid linker

peptide (linkers of 3 to 6 residues were examined and a linker of four residues was used in most cases).

D3 discloses methods of constructing modified forms of ligands such as IL-4 wherein the amino and carboxy ends are joined together, directly or through a linker, and new amino and carboxy terminal ends are formed at a different location within the ligand (see column 1). These circularly permuted ligands are used as a component in a fusion protein, in most cases, a toxin (column 2). Possible linkers are listed in column 4 and columns 11-12 (from 1 to 40 residues) and growth factors are listed also in column 4.

D4 discloses the circular permutation of the G-CSF agonist domain of myelopoietin.

D5 discloses methods of producing circularly-permuted proteins, in particular myelopoietin. Table 1 lists all known circularly permuted proteins (p. 26-7) and table 6 lists possible linkers.

In view of D1-D5, the subject-matter of claims 1, 2, 4-13, 24-27, 41-49, 53 is not considered new in the sense of Article 33(2) PCT.

The subject-matter of the remaining claims cannot be derived from the available prior art in an obvious manner and therefore complies with the requirements of Article 33(3) PCT.

Present claim 51 is directed to a product of the process of claim 49. The product of a process must be new and inventive per se, regardless of the process used to manufacture or identify it. However, the possible products identified by the process of claim 49 include an extremely large number of possible compounds/products. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/products claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search and examination over the whole of the claimed scope is impossible.